MEDICAL POLICY

POLICY TITLE	USE OF COMMON GENETIC VARIANTS (SINGLE NUCLEOTIDE POLYMORPHISMS) TO PREDICT RISK OF NON-FAMILIAL BREAST CANCER
POLICY NUMBER	MP 2.249

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**4/1/2024**

I. POLICY

Testing for one or more single nucleotide variants to predict an individual's risk of breast cancer is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The GeneType ® breast cancer risk test is considered **investigational** for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

POLICY GUIDELINES

Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing nomenclature for medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert

opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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GENE VARIANTS AND BREAST CANCER RISK

Rare, single-gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are variants in *BRCA1* and *BRCA2*. These, and a few others, account for less than 25% of inherited breast cancer. Moderate risk alleles, such as variants in the *CHEK2* gene, are also relatively rare and apparently explain very little of the genetic risk.

In contrast, several common single nucleotide variants (SNVs) associated with breast cancer have been identified primarily through genome-wide association studies of very large case-control populations. These alleles occur with high frequency in the general population, and the increased breast cancer risk associated with each is very small relative to the general population risk. Some have suggested that these common-risk SNVs could be combined for individualized risk prediction either alone or in combination with traditional predictors; personalized breast cancer screening programs could then vary by starting age and intensity according to risk. Along these lines, the American Cancer Society recommend that women at high risk (>20% lifetime risk) should undergo breast magnetic resonance imaging and a mammogram every year, and those at moderately increased risk (15%-20% lifetime risk) should talk with their doctors about the benefits and limitations of adding magnetic resonance imaging screening to their yearly mammogram.

Gene Type for Breast Cancer

GeneType for Breast Cancer (and the previous versions of the test, BREVAGenplus® and BREVAGen®) evaluates breast cancer-associated single nucleotide variants (SNVs) identified in genome-wide association studies. The first-generation test, BREVAGen, included 7 SNVs. Currently, GeneType includes over 70 SNVs. Risk is calculated by combining individual SNV risks with other risk factors. GeneType has been evaluated for use in African-American, Caucasian, and Hispanic patient samples, age 35 years and older, who do not have a history of

in situ or invasive breast cancer and are not carriers of a known pathogenic variant or rearrangement in a breast cancer susceptibility gene.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). GeneType for Breast Cancer (Genetic Technologies) is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence

For individuals who are asymptomatic and at average risk of breast cancer by clinical criteria who receive testing for common SNVs associated with a small increase in the risk of breast cancer, the evidence includes observational studies. Relevant outcomes are test validity, morbid events, and quality of life. Clinical genetic tests may improve the predictive accuracy of current clinical risk predictors. However, the magnitude of improvement is small, and clinical significance is uncertain. Whether the potential harms of these tests due to false-negative and false-positive results are outweighed by the potential benefit associated with improved risk assessment is unknown. Evaluation of this technology is further complicated by the rapidly increasing numbers of SNVs associated with a small risk of breast cancer. Long-term prospective studies with large sample sizes are needed to determine the clinical validity and utility of SNV-based models for predicting breast cancer risk. The discriminatory ability offered by the genetic factors currently known is insufficient to inform clinical practice. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member’s health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member’s health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational and therefore not covered for Non-BRCA Breast Cancer Risk Assessment GeneType ® as outlined in the policy statement.

Procedure Codes								
81599								

IX. REFERENCES

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POLICY TITLE	USE OF COMMON GENETIC VARIANTS (SINGLE NUCLEOTIDE POLYMORPHISMS) TO PREDICT RISK OF NON-FAMILIAL BREAST CANCER
POLICY NUMBER	MP 2.249

X. POLICY HISTORY

TOP

MP 2.249	**04/27/2020**- **Consensus review.** No changes to policy statements. References updated.
	11/23/2021 Consensus Review. Changed name from BREVAGenplus to GeneType but no change to intent or criteria. Update to policy guidelines, background, and references.
	11/14/2022 Consensus Review. No change in policy statement. References updated.
	1/5/2024 Consensus Review. No change to policy statement. Cross references and references updated.

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